Clinical trial results:
Multicenter, open label trial to investigate the efficacy and safety of a single oral dose of 1.0 mg/kg macimorelin acetate as growth hormone stimulation test (GHST) in pediatric patients with suspected growth hormone deficiency (GHD)

Summary

EudraCT number	2018-001989-42
Trial protocol	SI DE PL IT SK
Global end of trial date	13 June 2024

Results information

Result version number	v1 (current)
This version publication date	01 January 2025
First version publication date	01 January 2025

Trial information

Trial identification

Sponsor protocol code	AEZS-130-P02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04786873
WHO universal trial number (UTN)	U1111-1248-5075
Other trial identifiers	IND Number: 154015

Notes:

Sponsors

Sponsor organisation name	Aeterna Zentaris GmbH
Sponsor organisation address	Weismuellerstraße 50, Frankfurt am Main, Germany, D-60314
Public contact	Clinical trial information desk, Aeterna Zentaris GmbH, 0049 69426023472, clinical.trials@aezsinc.com
Scientific contact	Clinical trial information desk, Aeterna Zentaris GmbH, 0049 69426023472, clinical.trials@aezsinc.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001988-PIP01-16
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 August 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 June 2024
Global end of trial reached?	Yes
Global end of trial date	13 June 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the diagnostic efficacy of macimorelin in diagnosing suspected growth hormone deficiency (GHD) in pediatric subjects assuming the outcome of GHD status adjudication by the external adjudication committee as the "true" GHD status.

Protection of trial subjects:

Participants were closely monitored for adverse events, with safety assessments integrated into the protocol to promptly identify any issues requiring investigator intervention. At the same time, the frequency of assessments and visits was limited to essential procedures, balancing thorough safety oversight with minimising the burden on participants. Enrollment criteria and concomitant medications were defined to exclude participants with a high risk of events during the trial. To ensure adequate treatment also in emergency situations (e.g., allergic reaction), the investigator ensured test administration and participant observation in an adequate facility, with the required standards of treatment being available if required.
Additionally, several efforts were made to minimise the inconvenience to the participants during the trial. The fasting period was reduced to the extent possible; the investigators were encouraged to use numbing cream according to local practice to reduce the pain during peripheral venous access.

Background therapy:

Prepubertal boys >11 years and prepubertal girls >10 years underwent sex steroid priming before each GHST12. Both boys and girls should have received 2 mg (1 mg for body weight <20 kg) of β-estradiol orally on each of the two evenings preceding the test.

Evidence for comparator:

Besides the macimorelin GHST, arginine and clonidine standard GHSTs (sGHSTs) were performed. R-Gene 10 for the arginine GHST, and CATAPRESAN 75 for the clonidine GHST were administered as labelled IMP.
No direct comparison was performed between macimorelin GHST and the sGHSTs, but the results of the sGHSTs were considered to determine the diagnosis of growth hormone deficiency used to determine the diagnostic efficacy of the macimorelin GHST.

Actual start date of recruitment	22 March 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Romania: 10
Country: Number of subjects enrolled	Slovakia: 13
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 3

Country: Number of subjects enrolled	Armenia: 9
Country: Number of subjects enrolled	Georgia: 52
Country: Number of subjects enrolled	Serbia: 4
Country: Number of subjects enrolled	Türkiye: 4
Country: Number of subjects enrolled	United States: 20
Worldwide total number of subjects	125
EEA total number of subjects	36

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	73
Adolescents (12-17 years)	52
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial started on 16-Nov-2021 with the first informed consent signed. The first IMP (macimorelin GHST, V2) was administered on 14-Dec-2024. The trial was completed with Last-Subject-Last-Visit on 13-Jun-2024. Participants from Europe, the US, and the Caucasus and Anatolia region were enrolled.

Pre-assignment

Screening details:

Subjects were eligible if they met these criteria: informed consent from the subject, parent(s), or legally authorised representative (and assent if applicable); aged 2 to <18 years; required growth hormone stimulation testing; and had a height measurement 6–18 months before screening.

Pre-assignment period milestones

Number of subjects started	125
Number of subjects completed	102

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Inclusion/Exclusion Criteria not met: 15
Reason: Number of subjects	Subject withdrawal by parent or guardian: 3
Reason: Number of subjects	Withdrawal by subject: 5

Period 1

Period 1 title	Period of GHSTs (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	GHST sequence 1

Arm description:

Besides two macimorelin GHSTs, participants underwent sGHSTs in the randomized order of arginine and clonidine.

Arm type	GHST order
Investigational medicinal product name	Arginine
Investigational medicinal product code	
Other name	R-Gene® 10
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion , Intravenous use

Dosage and administration details:

After an overnight fast soluble arginine hydrochloride (0.5 g/kg) was given i.v. as an infusion with an infusion duration of 30 min.
Blood was collected for GH measurement, at altogether 4 sampling time points (pre-dose, and 30, 60, and 90 minutes after the end of the infusion).

Investigational medicinal product name	Clonidine
Investigational medicinal product code	
Other name	CATAPRESAN® 75
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

After an overnight fast clonidine (0.15 mg/m2 body surface) was given orally.
Blood was collected for GH measurement, at altogether 4 sampling time points (pre-dose, and 30, 60, and 90 minutes post-dose).

Investigational medicinal product name	Macimorelin
Investigational medicinal product code	
Other name	AEZS-130
Pharmaceutical forms	Oral powder in sachet
Routes of administration	Oral use

Dosage and administration details:

Macimorelin was supplied in single-use aluminum pouches, each containing 63.6 mg macimorelin as acetate, which provided 0.5 mg/mL of macimorelin when dissolved in 120 mL of water. Macimorelin oral solution/suspension was prepared by trial personnel by dissolving the entire contents of each pouch in 120 mL of water. The dose of macimorelin was 1.0 mg/kg body weight.
Macimorelin GHST was performed twice, before and after the sGHSTs, on separated visit days. Subjects were fasting for 8 hours prior to the start and throughout the sampling period of the macimorelin GHST.
Blood was collected for GH measurement, at altogether 5 sampling time points (pre-dose, and 30, 45, 60, and 90 minutes post-dose).

Arm title	GHST sequence 2

Arm description:

Besides two macimorelin GHSTs, participants underwent sGHSTs in the randomized order of clonidine and arginine.

Arm type	GHST sequence 2
Investigational medicinal product name	Clonidine
Investigational medicinal product code	
Other name	CATAPRESAN® 75
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

After an overnight fast clonidine (0.15 mg/m2 body surface) was given orally.
Blood was collected for GH measurement, at altogether 4 sampling time points (pre-dose, and 30, 60, and 90 minutes post-dose).

Investigational medicinal product name	Arginine
Investigational medicinal product code	
Other name	R-Gene® 10
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion , Intravenous use

Dosage and administration details:

After an overnight fast soluble arginine hydrochloride (0.5 g/kg) was given i.v. as an infusion with an infusion duration of 30 min.
Blood was collected for GH measurement, at altogether 4 sampling time points (pre-dose, and 30, 60, and 90 minutes after the end of the infusion).

Investigational medicinal product name	Macimorelin
Investigational medicinal product code	
Other name	AEZS-130
Pharmaceutical forms	Oral powder in sachet
Routes of administration	Oral use

Dosage and administration details:

Macimorelin was supplied in single-use aluminum pouches, each containing 63.6 mg macimorelin as acetate, which provided 0.5 mg/mL of macimorelin when dissolved in 120 mL of water. Macimorelin oral solution/suspension was prepared by trial personnel by dissolving the entire contents of each pouch in 120 mL of water. The dose of macimorelin was 1.0 mg/kg body weight.
Macimorelin GHST was performed twice, before and after the sGHSTs, on separated visit days. Subjects were fasting for 8 hours prior to the start and throughout the sampling period of the macimorelin GHST.
Blood was collected for GH measurement, at altogether 5 sampling time points (pre-dose, and 30, 45, 60, and 90 minutes post-dose).

Number of subjects in period 1[1]	GHST sequence 1	GHST sequence 2
Started	51	51
Completed	47	44
Not completed	4	7
Adverse event, non-fatal	1	2
Study Subject Withdrawal by Parent or Guardian	1	2
Non-Compliance With Study Drug	-	2
Not defined	2	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 23 Subjects were not randomized, only screened.

Baseline characteristics

Reporting groups	
Reporting group title	GHST sequence 1
Reporting group description:	
Besides two macimorelin GHSTs, participants underwent sGHSTs in the randomized order of arginine and clonidine.	
Reporting group title	GHST sequence 2
Reporting group description:	
Besides two macimorelin GHSTs, participants underwent sGHSTs in the randomized order of clonidine and arginine.	

Reporting group values	GHST sequence 1	GHST sequence 2	Total
Number of subjects	51	51	102
Age categorical Units: Subjects			
Children (2-11 years)	31	30	61
Adolescents (12-17 years)	20	21	41
Age continuous Units: years			
arithmetic mean	10.1	10.3	
standard deviation	± 3.32	± 3.49	-
Gender categorical Units: Subjects			
Female	12	12	24
Male	39	39	78
Pubertal status Units: Subjects			
Tanner I	33	33	66
Tanner II	14	11	25
Tanner III	3	5	8
Tanner IV	1	2	3
X-ray bone assessment age Units: year			
arithmetic mean	8.57	8.92	
standard deviation	± 3.963	± 3.592	-

Subject analysis sets	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects randomized.	

Reporting group values	FAS		
Number of subjects	102		
Age categorical Units: Subjects			
Children (2-11 years)	61		

Adolescents (12-17 years)	41		

Age continuous Units: years			
arithmetic mean	10.2		
standard deviation	± 3.39		
Gender categorical Units: Subjects			
Female	24		
Male	78		
Pubertal status Units: Subjects			
Tanner I	66		
Tanner II	25		
Tanner III	8		
Tanner IV	3		
X-ray bone assessment age Units: year			
arithmetic mean	8.74		
standard deviation	± 3.767		

End points

End points reporting groups

Reporting group title	GHST sequence 1
Reporting group description:	
Besides two macimorelin GHSTs, participants underwent sGHSTs in the randomized order of arginine and clonidine.	
Reporting group title	GHST sequence 2
Reporting group description:	
Besides two macimorelin GHSTs, participants underwent sGHSTs in the randomized order of clonidine and arginine.	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects randomized.	

Primary: Macimorelin ROC

End point title	Macimorelin ROC[1]
End point description:	
Assuming the outcome of GHD status adjudication final clinical diagnosis as the "true" GHD status, the diagnostic efficacy (estimated sensitivity, specificity, misclassification) of the macimorelin GHST was based on the area under the receiver operating characteristic curve (ROC AUC). ROC AUC based on peak GH levels (Cmax GH) after stimulation with macimorelin was estimated non-parametrically using the trapezoidal area under the empirical ROC plot. Based on the observed PK and PD data for macimorelin, which are in-line with previous data in children (trial AEZS-130-P01) and adults, the outcome of the efficacy analysis is surprising for the sponsor. Considering that macimorelin has been validated successfully as diagnostic test in the adult population, post-hoc analyses activities have been started to understand the reasons for the efficacy outcome. The final post-hoc analyses are not available yet at the time of finalization of this CTR.	
End point type	Primary
End point timeframe:	
Macimorelin GHST on visit 2.	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: This is a single-arm study with no statistical comparison of treatment arms.	

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	95			
Units: area				
number (confidence interval 95%)	0.762 (0.663 to 0.861)			

Attachments (see zip file)	Figure 14.2.1.1.pdf Figure 14.2.1.2.pdf Figure 14.2.5.1.pdf Figure 14.2.6.1.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Sensitivity for the macimorelin GHST

End point title	Sensitivity for the macimorelin GHST

End point description:

End point type	Secondary

End point timeframe:

Macimorelin GHST on visit 2.

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	95			
Units: %				
number (confidence interval 95%)	78.6 (63.2 to 89.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Specificity of macimorelin GHST

End point title	Specificity of macimorelin GHST

End point description:

End point type	Secondary

End point timeframe:

Macimorelin GHST on visit 2.

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	95			
Units: %				
number (confidence interval 95%)	67.9 (53.7 to 80.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall agreement between the outcome of the macimorelin GHST and the combined outcome from the 2 sGHSTs

End point title	Overall agreement between the outcome of the macimorelin GHST and the combined outcome from the 2 sGHSTs

End point description:

An overall agreement between the outcome of the macimorelin GHST and the combined outcome from the two sGHST was calculated.

End point type	Secondary

End point timeframe:

Macimorelin GHST on visit 2.

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	95			
Units: %				
number (confidence interval 95%)	65.3 (54.8 to 74.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the signature of ICF up to the end of the study (visit 6).

Adverse event reporting additional description:

Macimorelin, Arginine, and Clonidine reporting groups include AEs starting after the IMP drug administration up to the next GHST, last trial contact, or 7 days after the administration (whichever comes first).
In reporting group Total, all AEs reported during the study are reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27

Reporting groups

Reporting group title	Macimorelin
Reporting group description: -	
Reporting group title	Arginine
Reporting group description: -	
Reporting group title	Clonidine
Reporting group description: -	
Reporting group title	Total

Reporting group description: -

Serious adverse events	Macimorelin	Arginine	Clonidine
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Pharyngitis streptococcal			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 102 (0.98%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
Pharyngitis streptococcal			

subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Macimorelin	Arginine	Clonidine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 102 (11.76%)	6 / 97 (6.19%)	18 / 96 (18.75%)
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	3 / 102 (2.94%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	3	0	0
Amylase increased			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	10 / 96 (10.42%)
occurrences (all)	0	0	10
Diastolic hypotension			
subjects affected / exposed	1 / 102 (0.98%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 102 (0.00%)	1 / 97 (1.03%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Sinus bradycardia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	1 / 102 (0.98%)	1 / 97 (1.03%)	12 / 96 (12.50%)
occurrences (all)	1	1	12
Headache			

subjects affected / exposed	1 / 102 (0.98%)	0 / 97 (0.00%)	1 / 96 (1.04%)
occurrences (all)	1	0	1
Brain fog			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 102 (0.00%)	1 / 97 (1.03%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Hypothermia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Vaccination site reaction			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 102 (2.94%)	1 / 97 (1.03%)	0 / 96 (0.00%)
occurrences (all)	3	1	0
Abdominal pain upper			
subjects affected / exposed	1 / 102 (0.98%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	0 / 102 (0.00%)	1 / 97 (1.03%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 102 (0.00%)	1 / 97 (1.03%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Anorectal disorder			

subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 102 (1.96%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	2	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 102 (0.00%)	1 / 97 (1.03%)	1 / 96 (1.04%)
occurrences (all)	0	1	1
Dermatitis diaper			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Beta haemolytic streptococcal infection			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
COVID-19			
subjects affected / exposed	1 / 102 (0.98%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	1	0	0
Enterocolitis viral			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	1 / 96 (1.04%)
occurrences (all)	0	0	1

Upper respiratory tract infection			
subjects affected / exposed	0 / 102 (0.00%)	1 / 97 (1.03%)	0 / 96 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Blood bicarbonate decreased			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis Escherichia coli			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Laryngitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Pharyngotonsillitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0
Staphylococcal skin infection			
subjects affected / exposed	0 / 102 (0.00%)	0 / 97 (0.00%)	0 / 96 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Total		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	40 / 102 (39.22%)		
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	5 / 102 (4.90%)		
occurrences (all)	6		
Amylase increased			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Vascular disorders			
Hypotension			
subjects affected / exposed	11 / 102 (10.78%)		
occurrences (all)	11		
Diastolic hypotension			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	3 / 102 (2.94%)		
occurrences (all)	3		
Sinus bradycardia			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Nervous system disorders			
Somnolence			
subjects affected / exposed	14 / 102 (13.73%)		
occurrences (all)	14		
Headache			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences (all)	2		
Brain fog			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	1 / 102 (0.98%) 1		
Hypothermia subjects affected / exposed occurrences (all)	1 / 102 (0.98%) 1		
Pyrexia subjects affected / exposed occurrences (all)	3 / 102 (2.94%) 3		
Vaccination site reaction subjects affected / exposed occurrences (all)	1 / 102 (0.98%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	4 / 102 (3.92%) 4		
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 102 (0.98%) 1		
Nausea subjects affected / exposed occurrences (all)	1 / 102 (0.98%) 1		
Vomiting subjects affected / exposed occurrences (all)	2 / 102 (1.96%) 2		
Anorectal disorder subjects affected / exposed occurrences (all)	1 / 102 (0.98%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 102 (1.96%) 2		
Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 102 (0.98%) 1		
Skin and subcutaneous tissue disorders			

Dermatitis contact			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	2		
Dermatitis diaper			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Infections and infestations			
Beta haemolytic streptococcal infection			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
COVID-19			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences (all)	2		
Conjunctivitis			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Enterocolitis viral			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Blood bicarbonate decreased			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Ear infection			

subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Gastroenteritis Escherichia coli			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Laryngitis			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Pharyngotonsillitis			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences (all)	2		
Rhinitis			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		
Staphylococcal skin infection			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 September 2021	The overall rationale for the changes implemented in the amended protocol was to overcome inconsistencies between the flowchart, synopsis and the full text body, respectively. Furthermore, β-estradiol was being presented as NIMP supplied centrally to Non-USA based sites.
28 February 2024	The overall rationale for the changes implemented in the amended protocol was to update the number of sites and list of countries involved in this trial, to update the contact information for service providers, and to introduce the collection of certified redacted paper ECG copies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Considering that macimorelin has been validated successfully as diagnostic test in the adult population, post-hoc analyses activities have been started to understand the reasons for the efficacy outcome.

Notes: